PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

First Named Inventor: Bandi PARTHASARADHI REDDY

Serial No: 10/509,952 — Group Art Unit: 1625

Filed: 10/04/2004 — Examiner: CHANG, CELIA C

Att. Docket No.: H1089/20015 — Confirmation No.: 3097

For: NOVEL PROCESS FOR AMORPHOUS FORM OF DONEPEZIL HYDROCHLORIDE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INTRODUCTORY COMMENTS

Applicant(s) hereby request(s) review of the Final Rejection in the above-identified application.

No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s) entitled Remarks/Arguments. The Remarks/Arguments section does not exceed five pages in length.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

July 10, 2008

By _____
Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicant(s)

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

196201_1

REMARKS/ARGUMENTS IN SUPPORT OF THE PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action dated January 17, 2008, favorable reconsideration is respectfully requested in view of the following remarks. A Notice of Appeal in compliance with 37 C.F.R. § 41.31 is filed concurrently herewith.

ERRORS IN THE EXAMINER'S REJECTIONS UNDER 35 U.S.C. § 102(e)

The rejection of claims 1 and 4 under 35 USC 102(e) over US 6,649,765 (Vidyadhar) has been maintained. This rejection is respectfully traversed.

The claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent yielding amorphous donepezil hydrochloride.

The Examiner cites two chemical handbooks to define terms. However, this 102(e) rejection was first made in the Non-Final Office Action of August 10, 2007. In the Reply filed November 11, 2007, Applicant did not amend the claims, and these claims remain in the form they were in for the Non-Final Office Action of August 10, 2007. The Examiner has added these two references, but has made this Office Action final. This is improper. Applicant has not had an opportunity to respond to the newly cited references. Therefore, since these limitations had been pending and under consideration previously, it was improper for the Examiner to have made this action Final, especially given that newly cited art was applied. The newly cited art was not necessitated by Applicant's amendment, as these limitations had been previously considered. Accordingly, reconsideration and withdrawal of the Finality of the Office Action of January 17, 2008 is respectfully requested. MPEP 706.07(d).

In addition, the Examiner argues that the CRC handbook defines "amorphous" as "having no definite order of crystalline structure", and concludes that a solid was not defined to have

"definitive crystalline order" is amorphous. The Examiner further cites the Hackh's chemical dictionary to show that the term "concentrate" chemically is the increase of solute content, thus, not removal of all solvent, and further states that the misinterpretation of the terms by the attorney is improper.

However, while the Examiner argues that a solid being silent about its crystallinity is noncrystalline or amorphous, the cited art does not stand for this proposition. The art newly cited by the Examiner simply defines the term "amorphous". It does not teach that a solid that was not defined to have "definitive crystalline order" is amorphous. If the Examiner is arguing that the '765 Vidyadhar patent inherently discloses the amorphous form of donepezil hydrochloride as instantly claimed, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. Here, the Examiner has not shown that the missing descriptive matter is necessarily present in the thing described in the reference.

Accordingly, reconsideration and withdrawal of the rejection of claims 1 and 4 under 35 USC 102(b) is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTIONS UNDER 35 U.S.C. § 103

The rejection of claims 1-4 under 35 USC 103 (a) over Vidyadhar et al. '765 in view of Imai '864 or over Sugimoto et al. '841 or Vidyadhar et al. '765 or Imai in view of Lieberman and Brittain has been maintained. This rejection is respectfully traversed.

The Examiner argues that (Office Action at pages 2-3):

> Applicants provided no factual evidence that why a process employed a simultaneously co-existed mixture of chlorinated solvent and alcohol would produce an amorphous material which is different from the noncrystalline solid found in the prior art using a stepwise introduced dichloromethane and methanol solvents, when both solvents are known to dissolve donepezil hydrochloride.

However, the claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the

donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. So, there is not a disclosure in the '765 Vidyadhar patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. This deficiency is not addressed by the '864 Imai patent.

While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent which is selected from the group consisting of chloroform, methylene dichloride, carbontetrachloride and ethylene dichloride.

The Examiner argues the motivation is provided in that one having ordinary skill in the art in possession of general laboratory skill and the Imai et at '864 reference would be in possession of the instant claims because a proven process was disclosed by Vidyadhar '765, the optional choices of solvents wherein donepezil hydrochloride is soluble have been provided by Imai, and that therefore, one having ordinary skill would pick and choose any of the solvent or mixture of solvents wherein donepezil hydrochloride is soluble for the process and employ anyone of the solvent removing technique for solvent reduction depending on resource availability. However, as set forth above, the '765 Vidyadhar patent does not teach or suggest donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent, and this is also not taught or suggested in the '864 Imai patent. Since the combination of the patents does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

In addition, the rejection under 35 USC 103 over Sugimoto et al. US 4,895,841 or Vidyadhar et al. US 6,649,765, or Imai et al. US 5,985,864 in view of Lieberman et al. and Brittain is respectfully traversed.

Here, not every element of the claims is taught or suggested in the combination of the references. As set forth above, the claims are drawn to a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. This is in contrast to

the disclosure of the '765 Vidyadhar patent. Example 2 of the '765 Vidyadhar patent discloses preparing donepezil free base in methylene chloride, then removing the methylene chloride. In an additional step, the donepezil free base is dissolved in methanol, followed by addition of hydrochloric acid. Accordingly, there is not a teaching or suggestion in the '765 Vidyadhar patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. In addition, there is not a teaching or suggestion in the '841 Sugimoto patent of donepezil hydrochloride dissolved in a mixture of an alcohol and a chlorinated solvent. Example 4 of the '841 Sugimoto patent as cited by the Examiner discloses donepezil base dissolved in methylene chloride, to which a 10% solution of hydrochloric acid in ethyl acetate is added, followed by concentration *in vacuo* to obtain a crystal, which was recrystallized from methanol/isopropyl ether. This deficiency is not addressed by the '864 Imai patent. While the '864 Imai patent discloses several polymorphs of donepezil hydrochloride, it does not teach or suggest amorphous donepezil hydrochloride prepared by dissolving donepezil hydrochloride in a mixture of an alcohol and a chlorinated solvent. The '864 Imai patent does not teach or suggest a chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride.

In addition, there is no motivation for one of skill in the art to alter the methods of the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the Lieberman and Brittain references to alter the methods as taught by the '841 Sugimoto patent, the '765 Vidyadhar patent, or the '864 Imai patent to arrive at the instantly claimed method.

The Examiner argues the motivation is provided in that one having ordinary skill in the art in possession of the purified crystalline or solid material of the compound donepezil hydrochloride would be motivated to prepare an amorphous form of the product because it is conventional state of the art that "[t]heoretical considerations predict that amorphous solids will in general, be better absorbed than will crystalline ones" (see Lieberman p. 463) and the procedure for obtaining amorphous forms have been conventionally well delineated using a spray drying or vacuum drying process (Brittain). The Examiner further argues that the claims would have been obvious because an ordinary skilled person "has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is

likely the product not of innovation but of ordinary skill and common sense." KSR 82 USPQ2d 1385, 1390. However, in the KSR case, the Court noted that the analysis supporting a rejection under 35 USC 103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". KSR, slip op. at 15.

Here, there is not a combination of prior art elements, since no reference, or combination of references, teaches or suggests a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution. No reference or combination of references teaches or suggests such a method wherein the chlorinated solvent is chloroform, methylene dichloride, carbontetrachloride or ethylene dichloride. In addition, Applicant has shown that there is not a reason why a person of ordinary skill in the art would be motivated to practice a process for preparing donepezil hydrochloride wherein donepezil hydrochloride is dissolved in a mixture of an alcohol and a chlorinated solvent and then the solvents are removed from the solution.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4 under 35 USC 103(a) is respectfully requested.

* * *

Accordingly, the Pre-Appeal Brief Conference Panel is respectfully requested to withdraw the appealed rejection(s) and pass this application on to issuance.